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III.

CONTRIBUTIONS FROM THE CHEMICAL LABORATORY OF
HARVARD COLLEGE.

I.—ON THE ETHERS OF URIC ACID.

BY H. B. HILL.

(First Paper.)

Presented, June 14, 1876.

ALTHOUGH the constitution of many of the derivatives of uric acid may be said to be fairly established, the structure of uric acid itself is still a matter of conjecture. The formulæ given by Baeyer,* Kolbe,† Strecker‡ Erlenmeyer,§ Mulder,|| Hüfner,¶ Gibbs,** Medicus,†† Drechsel,‡‡ and Mallet; §§ differing, as they do, in points more or less essential, show that the experimental data are as yet insufficient to establish its structure. In this connection the ethers of uric acid seem to have attracted little attention. In 1864, Drygin |||| prepared the diethyl and triethyl ethers by the action of ethyl iodide upon diplumbic urate. I have been unable to obtain the original paper, but from the summary of it given in the Jahresbericht ¶¶ for that year, and in Gmelin's *** hand-book, it would appear that he submitted them to no very extended examination. I have, therefore, undertaken the study of the ethers of uric acid, with the hope that a careful study of the products

* Ann. Chem. u. Pharm., 127, 235.

† Journ. für prakt. Chem. [2] 1. 134. Berichte, Deutsch. Chem. Gesellsch. III. 183.

‡ Zeitschr. für Chem. 1868, 363.

§ Zeitschr. für Chem. 1869, 176. München. Acad. Ber. 2, 276.

|| Bericht. der Deutsch. Chem. Gesellsch. VI. 1237.

¶ Journ. für prakt. Chem. [2] 3, 23.

** Amn. Journ. [2] 46, 289.

†† Ann. Chem. u. Pharm. 175, 243.

‡‡ Chem. Centralbl. 1875, 493.

§§ Amn. Journ. Mch. 1876, 195.

|||| Russ. Zeitschr. Pharm. ii. 3, 28, 49, 113, 121.

¶¶ Jahresbericht. 1864, 629.

*** Gmelin, Suppl. ii. 1026.

of their decomposition may throw additional light upon the structure of uric acid.

A few preliminary experiments convinced me that the compounds in the methyl series could be much more conveniently made than those of the ethyl or benzyl. I therefore began with the methyl ethers, and this paper gives the results I have obtained in the study of the first of these.

Methyluric acid, $C_5H_3(CH_3)_4N_4O_3$.

Methyluric acid may readily be prepared by the action of methyl iodide upon monoplumbic urate. The metathesis takes place slowly at 110° – 130° , rapidly between 160° and 165° . The dry lead salt mixed with methyl iodide in molecular proportions, enough ether being added to keep the mixture fluid, is heated in sealed tubes for eighteen hours at 165° . After the evaporation of the ether, the product of the reaction is boiled with water, and the solution filtered from the unaltered plumbic urate. The lead is then precipitated with hydric sulphide, and the plumbic sulphide filtered off boiling hot. The filtrate deposits, on cooling, methyluric acid in small crystals. These are dissolved in dilute potassic hydrate, the solution boiled for a few minutes, reprecipitated by hydrochloric acid, and recrystallized from boiling water. The yield is about 60% of the amount theoretically required by the lead salt which enters into the reaction. 220 grms. plumbic urate gave 54 grms. methyluric acid, and 89 grms. of unaltered lead salt. Afterwards, in working up the recovered lead salt, which was much more compact in form than the salt originally employed, I found the decomposition almost complete. In this case 100 grms. lead salt gave me 41 grms. methyluric acid. A portion of the uric acid is completely decomposed, and is found as ammonium salt in the mother liquors and the crude product. I attempted to increase the yield by employing anhydrous ether in the place of common ether. Although no ammonium compounds were then formed, a much smaller percentage of the lead salt entered into reaction. Longer heating at a lower temperature did not increase the yield, inasmuch as a larger quantity of dimethyl ether was then formed. The amount of dimethyl ether formed by heating to 165° is small; and as it is much more soluble in water than the monomethyl ether, it may readily be removed by recrystallization.

Methyluric acid crystallizes in small clear flat prisms, apparently of the trimetric system, the crystals being often pointed at either end. By slow cooling of a dilute solution, these crystals sometimes reach a

length of 2–3 mm., but they are usually much smaller. The substance undergoes no visible change when heated to about 300° ; at a higher temperature, it melts with complete decomposition, and without perceptible sublimation. It is soluble in boiling water, almost insoluble in cold water or in boiling alcohol; insoluble in ether. Cold concentrated sulphuric acid dissolves it abundantly; upon dilution it crystallizes out, apparently unchanged. Air-dried it contains water, a portion of which it loses at 100° ; the rest slowly, but completely, at 160° .

1.3887 grm. substance air-dried lost at 165° 0.1124 grm. = 8.09%.

The formula $C_5H_3(CH_3)N_4O_3 \cdot H_2O$ requires 9.00%. Of substance dried at 100° :—

1.	0.7772 grm. lost at 165°	0.0399 grm. = 5.13 %.
2.	0.4953 " "	0.0289 " = 5.83 %.
3.	0.4670 " "	0.0238 " = 5.10 %.
4.	0.8106 " "	0.0451 " = 5.57 %.

The formula $C_5H_3(CH_3)N_4O_3 \cdot \frac{1}{2}H_2O$ requires 4.77%.

From these determinations, it would appear that water is not a definite constituent of the compound. The microscopic appearance of the substance remains unchanged.

The substance dried at 165° has the formula $C_5H_3(CH_3)N_4O_3$, as the following analyses show:—

- 0.4284 grm. gave 0.1310 grm. H_2O , and 0.6210 grm. CO_2 .
- 0.2748 grm. gave 0.0985 grm. H_2O , and 0.3972 grm. CO_2 .
- 0.1822 grm. gave 50.0 cc. nitrogen, at $20^{\circ}.5$, and 754.3 mm. pressure.

Calculated for		Found.		
$C_5H_3(CH_3)N_4O_3$.		1	2	3
C	39.56	39.53	39.43	
H	3.30	3.39	3.98	
N	30.77			30.98

To determine the solubility in boiling water, a boiling saturated solution was filtered through a hot water filter into tared flasks. After cooling, the flasks were weighed, the contents washed out, evaporated in platinum, and the residue dried at 165° .

- 52.290 grm. solution left 0.2043 grm. residue.
- 55.379 grm. solution left 0.2187 grm. residue.

The boiling saturated solution contains, therefore, the percentages, —

1	2
0.3906	0.3950

A boiling solution was allowed to stand overnight at a temperature of about 20°. For three hours before filtering, it was kept at 20°, with constant stirring. Portions of the filtered solution were weighed, evaporated, and the residue dried at 165°, —

1. 39.020 grm. solution gave 0.0083 grm. residue.
2. 49.854 grm. solution gave 0.0111 grm. residue.

The solution saturated at 20° contained, therefore, in percentages, —

1	2
0.0213	0.0223

As the mean of these determinations, we find that there is required for the solution of one part of methyluric acid 253.6 parts of boiling water, and 4596 parts of water at 20°.

The aqueous solution reddens litmus feebly, and decomposes carbonates readily on heating. A solution in potassic or sodic hydrate is not precipitated by carbonic dioxide. From a concentrated cold solution, stronger acids precipitate it gelatinous, from hot or dilute solutions crystalline.

With bases methyluric acid forms a series of definite salts, some of which have been studied by Mr. O. R. Jackson in this laboratory. The results of this investigation he presents to the Academy in a separate communication. He has shown that the monomethyl ether of uric acid is itself a dibasic acid, like uric acid; a fact which is certainly remarkable, and of obvious theoretical importance.

Action of Hydrochloric Acid.

In 1867, Strecker * showed that uric acid heated with fuming hydrochloric or hydriodic acid to 170° assimilates five molecules of water, giving carbonic dioxide, ammonia, and glyccoll, —



The inferences which he drew † from this reaction concerning the structure of uric acid are well known. Emmerling ‡ has recently shown that cyanogen gas passed into boiling hydriodic acid is converted into glyccoll, and seeks thus to give Strecker's reaction a new interpretation. In either case, however, it seemed to me of importance to

* Ann. Chem. u. Pharm. 146, 142; Zeitschr. für Chem. 1868, 215.

† Zeitschr. für Chem. 1868, 363.

‡ Berichte Deutsch. Chem. Gesellsch. VI. 1351.

determine the products of the decomposition of methyluric acid under these conditions.

Two tubes, each containing 1.3 grm. methyluric acid, and an excess of hydrochloric acid saturated at 0°, were heated four or five hours at 170°. The gas which escaped on opening the tubes was found to contain no methyl chloride. The excess of acid was driven off on the water bath, and the residue distilled with plumbic hydrate until the distillate was no longer alkaline. The ammoniacal distillate was caught in hydrochloric acid, and evaporated to dryness on the water bath. The residue was treated with a small quantity of absolute alcohol, and the filtered solution again evaporated to dryness. There was then left a white saline residue, which gave with great readiness Hofmann's isocyanide reaction, showing the presence of a monamine. The chloride was converted into the platinum salt, and this was analyzed after recrystallization from hot water.

0.4760 grm. gave on ignition 0.1991 grm. platinum.

	Calculated for	Found.
	$(\text{CH}_3\text{NH}_2)_2\text{PtCl}_6$	
Pt	41.61	41.82

Methylamine is, therefore, one of the products of the reaction.

From the residue left on distillation, it was easy to isolate glycooll in the ordinary way. The liquid was filtered from the basic plumbic chloride, the lead removed from the solution by hydric sulphide, and the filtrate evaporated. On standing, glycooll crystallized out with its characteristic properties. For its identification, it was converted into the copper salt by boiling with freshly precipitated cupric oxide, and precipitation of the blue solution by alcohol. Of this salt, —

0.4400 grm. lost at 130° 0.0388 grm.

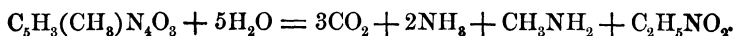
	Calculated for	Found.
	$(\text{C}_2\text{H}_4\text{NO}_2)_2\text{Cu} \cdot \text{H}_2\text{O}$	
H ₂ O	7.85	7.68

A determination of copper in the dry salt gave, —

0.4068 grm. left on ignition 0.1523 grm. CuO.

	Calculated for	Found.
	$(\text{C}_2\text{H}_4\text{NO}_2)_2\text{Cu}$	
CuO	37.55	37.43

The reaction in this case may therefore be written, —



It will be seen that this reaction proves the commonly accepted view that uric acid is not an hydroxyl but an imid acid.

In order further to establish the relative position of the methyl radical, it seemed to me of chief importance to follow it through oxidation in alkaline and acid solution, and thus determine its relation to allantoin and alloxan or paraban.

Methylallantoin. $C_4H_5(CH_3)N_4O_3$.

Methyluric acid is readily oxidized in alkaline solution, according to the method of Claus and Emde.* The solution must be dilute with but a small excess of alkali, the potassic permanganate added slowly in exact molecular proportion. As soon as the manganese dioxide has separated, it must be filtered rapidly with the aid of the pump, and the filtrate slightly acidified with acetic acid. I then found it most advantageous to evaporate as quickly as possible on the water bath to small volume. After standing twenty-four hours, the methylallantoin crystallizes out in clusters of radiated prisms. These separated from the mother liquor by pressure, and recrystallized several times from hot water, form clear distinct monoclinic prisms, closely resembling ordinary allantoin. They are readily soluble in hot water, sparingly in cold; almost insoluble in alcohol, hot or cold, and insoluble in ether. These crystals melt with decomposition at 225° .

In spite of many variations of the method, I could obtain in this way but fifteen per cent of the theoretical yield. From the mother liquors evaporated to a syrup, alcohol separates a potash salt, probably of methylallantoic acid. On account of its uninviting character it was not further examined.

Methylallantoin dried at 100° gave, on analysis, —

0.2362 grm. gave 0.1092 grm. H_2O , and 0.2978 grm. CO_2 .

	Calculated for	Found.
	$C_4H_5(CH_3)N_4O_3$.	
C	34.89	34.39
H	4.65	5.13

Silver nitrate gives in a hot saturated solution on the cautious addition of ammoniac hydrate, a crystalline precipitate consisting of needles or short prisms. This salt is readily soluble in hot water, more sparingly in cold. By spontaneous evaporation of the cold solution,

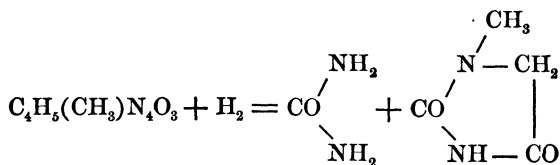
* Berichte Deutsch. Chem. Gesellsch. VII. 226.

tolerably perfect crystals of the trimetric system were obtained. This compound may be dried, without decomposition, at 100° , and gave then on analysis, —

0.1668 grm. left on ignition 0.0646 grm. silver.

	Calculated for	Found.
	$\text{AgC}_4\text{H}_4(\text{CH}_3)\text{N}_4\text{O}_8$.	
Ag	38.71	38.61

Baeyer * has shown that allantoin, when heated with hydriodic acid, breaks up into urea and hydantoin; and it was evident that methylallantoin should give an analogous reaction. I therefore heated methylallantoin with concentrated hydriodic acid, following the directions given by Baeyer.† When the reaction appeared to be ended, the liberated iodine was reduced with sulphide of hydrogen, and the hydriodic acid removed by plumbic carbonate. The filtrate gave on evaporation, after standing for some time, clear crystals, which, freed from the syrupy mother liquor, and recrystallized from water, formed transparent prisms, readily soluble in water or alcohol, and giving no precipitate with zincic chloride. Their melting point I found to be 144° – 145° . The quantity at my disposal was insufficient for analysis, but there can be no doubt of the identity of this substance with methylhydantoin described by Neubauer ‡ as resulting from the action of baric hydrate upon creatinine, inasmuch as he gives these properties and the melting point 145° . The reaction may, therefore, be written, —



Once, as the action of the hydriodic acid was longer continued, I obtained a substance crystallizing in broad rhombic plates, readily soluble in water, sparingly soluble in alcohol, which gave a precipitate with an alcoholic solution of zincic chloride. These crystals melted at 105° , and sublimed readily at 100° . They were evidently sarcosine formed from the decomposition of methylhydantoin.

* Ann. Chem. u. Pharm. 117, 178.

† Ann. Chem. u. Pharm. 130, 158.

‡ Ann. Chem. u. Pharm. 137, 288.

Oxidation of methyluric acid with nitric acid.

By the oxidation of methyluric acid with nitric acid, a solution is obtained which gives a deep red coloration on warming with ammoniac hydrate. From this solution, however, I have as yet been unable to isolate a crystalline product. By spontaneous evaporation in the air, a sticky syrup is obtained, which does not solidify, even after long standing *in vacuo* over sulphuric acid. Alcohol dissolves this residue, the solution remains clear after the addition of ether, and on evaporation again leaves an uncrystallizable syrup. I have been equally unsuccessful in separating by stannous chloride or sulphide of hydrogen a crystalline alloxantine or dialuric acid. Oxidation with potassic chlorate and hydrochloric acid, according to the method of Schlieper,* gave the same result. These reactions were sufficient to give a qualitative proof that the solution did not contain ordinary alloxan. I therefore attempted to prepare from this solution a methylalloxanate in form fit for analysis. I first tried with baric hydrate to form the barium salt. The ordinary method, following closely the directions of Schlieper,† gave me, however, a salt containing but a trace of nitrogen and with percentages of barium, carbon, and hydrogen, closely approximating those required by a basic baric mesoxalate, $\text{BaC}_3\text{O}_5 \cdot \text{BaO}_2\text{H}_2$. At the same time a strong smell of methylamine was perceived. If a smaller quantity of baric hydrate were added in the cold, and then alcohol in excess, a barium salt was thrown down which contained nitrogen, but it could not in this way be obtained of constant composition. Plumbic hydrate seemed to determine the formation of the methylalloxanate, but no better results were obtained. The silver salt blackened too rapidly to admit of analysis.

The lime salt is the only one I have been able to prepare with constant composition. Methyluric acid is dissolved in as small a quantity of nitric acid of 1.42 sp. gr. as possible, the solution somewhat diluted, and the excess of acid neutralized with calcic carbonate in the cold. The solution is then allowed to stand *in vacuo* for some time, to free it from carbonic dioxide, afterwards diluted with six or eight volumes of alcohol and filtered. The cautious addition of ammoniac hydrate to the filtrate throws down a bulky semigelatinous precipitate, which, well washed with alcohol, and dried at 100° , forms an amorphous powder, which has a faint pink color, — undoubtedly caused by a trace of alloxan. The dry salt was soluble in cold water, though with some difficulty.

* Ann. Chem. u. Pharm. 55, 261.

† Ann. Chem. u. Pharm. 55, 272.

Analysis gave for substance dried at 100°, —

1. 0.1778 grm. gave 0.1125 grm. CaSO_4 .
2. 0.2275 grm. gave 0.1446 grm. CaSO_4 .
3. 0.3049 grm. gave 36.8 cc. nitrogen at 21°.5, and 762.1 mm. pressure.

	Calculated for	Found.	
	$\text{C}_4\text{H}(\text{CH}_3)_2\text{N}_2\text{O}_5\text{Ca}$	1	2
			3
Ca	18.87	18.61	18.69
N	13.21		13.68

The analyses 1 and 2 were made with different preparations.

If ammoniac hydrate be first added, and the calcic salt then precipitated by alcohol, the salt contains too little nitrogen. A sample prepared in this way gave, on analysis, 20.88 % Ca, and 10.75 % N. So also if the precipitate thrown down by ammoniac hydrate in alcoholic solution be dissolved in water, and reprecipitated by alcohol, the percentage of calcium is increased, and the nitrogen diminished. Analysis gave 20.49 % Ca.

Inasmuch as the chief point was to prove the formation of methylalloxan by this oxidation, I distilled the calcium salt, prepared in the manner described, with potassic hydrate in a current of steam. The ammoniacal distillate readily gave the characteristic isocyanide reaction by heating with alcoholic potash and chloroform. It was neutralized with hydrochloric acid, evaporated, and from the residue the methylamine chloride separated by absolute alcohol. An analysis of the platinum salt gave —

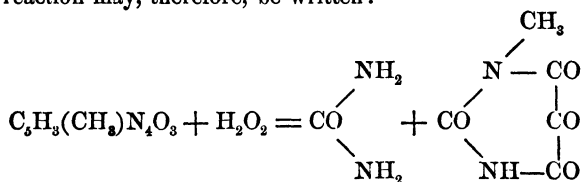
0.2160 grm. left on ignition 0.0902 grm. platinum.

	Calculated for	Found.
	$(\text{CH}_3\text{NH}_3)_2\text{PtCl}_6$	
Pt	41.61	41.76.

Thus proving that the calcium salt contained the group $=\text{N}-\text{CH}_3$.

In further confirmation, I was able to isolate common urea as the secondary product of the methylalloxan formation. After oxidizing with hydrochloric acid and potassic chlorate, the excess of acid was driven off by evaporation at gentle heat, the potassic chloride separated with absolute alcohol, and the alcoholic solution evaporated to a syrup. The cautious addition of strong nitric acid caused the separation of abundant crystals of urea nitrate in characteristic form. The base, set free as usual with baric carbonate, after recrystallization from water, melted at 129°–130°.

The reaction may, therefore, be written:—



Methylparaban, $\text{C}_3\text{H}(\text{CH}_3)\text{N}_2\text{O}_3$.

Although methylalloxan is so unstable in the presence of bases, in acid solution it possesses remarkable stability. It may be boiled for some time with strong nitric acid, or with hydrochloric acid and potassic chlorate before the red coloration with ammonia disappears. On prolonged boiling (about an hour) with strong nitric acid, the oxidation is complete, and the solution contains methylparaban. For its preparation I have found it most advantageous to boil methyluric acid with five or six parts of nitric acid of sp. gr. 1.3, until a drop taken out gives no coloration with ammonia. The excess of acid is then driven off on the water bath, the syrupy residue diluted with a little water, and well shaken out with ether. On distilling off the ether, a syrup remains which soon crystallizes in shining radiated prisms, which are recrystallized from hot water. They are somewhat difficultly soluble in cold water, readily in hot; soluble in alcohol and ether. The substance melts at $149^\circ.5$, sublimes very slowly at 100° , and at higher temperature with great readiness. For analysis, the air-dried substance was heated three hours at 100° ; during that time 0.2260 grm. lost 0.0030 grm.

1. 0.1714 grm. gave 0.2333 grm. CO_2 .*
2. 0.2160 grm. gave 0.0785 grm. H_2O , and 0.2629 grm. CO_2 .

	Calculated for	Found.	
	$\text{C}_4\text{N}_2\text{H}_4\text{O}_3$	1	2
C	37.50	37.12	37.48
H	3.13		4.04

The substance gives no precipitate with calcic chloride, even after the addition of ammoniac hydrate. On warming the ammoniacal solution, a precipitate falls not wholly soluble in acetic acid. Argentic nitrate precipitates it only in concentrated solution. The silver salt prepared from concentrated solution, with the cautious addition of

* The hydrogen in this analysis was lost.

ammonic hydrate, crystallizes in prismatic needles; quite readily soluble in hot water, sparingly in cold. Under the microscope it crystallizes from hot aqueous solution in rhombic plates. It may be dried at 100° without decomposition. It gave on analysis, —

0.1210 grm. left on ignition 0.0556 grm. silver.

	Calculated for	Found.
	$\text{AgC}_4\text{N}_2\text{H}_3\text{O}_3$.	
Ag	45.95	45.95

There can be no doubt that this substance is identical with that obtained by Dessaignes* from creatinine, which was first recognized by Strecker† as methylparaban. Dessaignes gives no melting point, but the description given corresponds perfectly with the substance I have obtained; the only difference being that I find the substance quite readily soluble in ether, whereas he gives it as somewhat soluble only.

A consideration of the bearing of these facts upon the structure of uric acid I shall postpone until I have obtained further results.

II.—ON SOME OF THE SALTS OF METHYLURIC ACID, $\text{C}_6\text{H}_3(\text{CH}_3)\text{N}_4\text{O}_3$.

BY OSCAR R. JACKSON.

Presented, June 14, 1876.

THIS work was undertaken with the purpose of proving the basicity of methyluric acid. The acid was obtained by the method described by Prof. H. B. Hill, under whose direction the preparation and analyses of the salts were conducted.

Owing to the fact that all the dibasic salts absorb carbonic acid very readily when exposed to air, as is the case with the salts of uric acid, special means had to be taken to dry the salts in an atmosphere free from carbonic acid. For this purpose they were dried *in vacuo* over sulphuric acid, and a few pieces of potassic hydrate were also placed under the receiver when the dibasic salts were dried. For the determination of the water of crystallization, the salts were heated to

* Ann. Chem. u. Pharm. 97, 343.

† Ann. Chem. u. Pharm. 118, 164.